REMARKS

With this response, claims 1-7, 10-12, 15-17, and 27-35 are pending. The specification has been amended to remove browser-extractable code and to correct minor typographical errors. No new matter enters by way of the present amendment. Based on the foregoing amendment and following remarks, Applicants respectfully request reconsideration and withdrawal of all outstanding objections and rejections.

I. Change in Examiner and Art Unit

Applicants hereby acknowledge the change in Examiner and Art Unit, and will note such change in all future correspondence with the U.S. Patent and Trademark Office.

II. Restriction Requirement

Applicants hereby acknowledge with appreciation the withdrawal of the Restriction Requirement mailed December 24, 2001.

III. Objection to the Specification

The disclosure has been objected to due to the presence of embedded hyperlinks and/or other browser-extractable code. Applicants have amended the specification to remove any reference to "http://", and have removed all embedded hyperlinks. As such, withdrawal of this objection is respectfully requested.

IV. Claim Rejections under 35 U.S.C. § 103(a)

A. Rejection over Cho *et al.* in view of Lai *et al.*

Claims 4, 6, 17, 29, 30, 31, 33, and 34 stand rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Cho *et al.* in view of Lai *et al.* This rejection is respectfully traversed and reconsideration is requested for at least the reasons that follow.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching

or suggestion to make the claimed combination must be found in the prior art, and not be based on applicants' disclosure. *See* M.P.E.P. §§2143.01 and 2143.03.

In a proper obviousness determination, the changes from the prior art must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the claimed invention. *See In re Chu,* 36 U.S.P.Q.2d 1089, 1094 (Fed. Cir. 1995). This includes what could be characterized as simple changes. *See, e.g., In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (Although a prior art device could have been turned upside down, that did not make the modification obvious unless the prior art fairly suggested the desirability of turning the device upside down.).

Only when the prior art teaches or suggests the claimed invention does the burden fall on the applicant to rebut that *prima facie* case. *See In re Dillon,* 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (in banc), *cert. denied,* 500 U.S. 904 (1991). However, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.

The present invention is drawn to a method of identifying a region of genomic DNA associated with a phenotypic trait of interest in *Arabidopsis* plants capable of detecting a set of polymorphisms that are distributed throughout the genome of *Arabidopsis* plants at an average density of more than one polymorphism per about 100 kb.

The Examiner asserts that Cho *et al.* teach a method of identifying a region of genomic DNA associated with a phenotypic trait of interest. However, as the Examiner also notes, Cho *et al.* do not specifically teach or suggest that the disclosed method is capable of detecting a set of polymorphisms that are distributed throughout the genome of *Arabidopsis* plants at an average density of more than one polymorphism per about 100 kb. Lai *et al.* discloses a high density SNP map of a portion of the human genome, where the map has a density of one SNP every 30 kb, and teach that such a map was generated "efficiently and rapidly" using existing methodologies. Whatever else Cho *et al.* and Lai *et al.* do disclose or suggest, they do not disclose or suggest an SNP map of *Arabidopsis* with a density of more than one polymorphism per about 100 kb.

The Examiner has alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the methods taught by Lai *et al.*, in order to produce a denser SNP map for use in the identification of a region of genomic DNA associated with a phenotypic trait of interest as taught by Cho *et al. Office Action at page 4.* The Examiner asserts that the ordinary practitioner would have been motivated to provide such a method by the suggestion of Cho *et al.* that "[t]he generation of denser biallelic maps should allow high-throughput identification of both monogenic and polygenic traits, effectively removing the rate-limiting nature of high resolution mapping from the study biological processes (p. 205)." The Examiner claims that the ordinary practitioner would have been further motivated by the teachings of Lai *et al.* that the generation of SNP-based maps can be accomplished "efficiently and rapidly" using existing methodologies. *Id.*

The mere fact that references can be modified does not render the resultant modification obvious unless the prior art also suggests the desirability of the modification. M.P.E.P. § 2143.01; *In re Mills,* 16 U.S.P.Q.2d 1430, 1432 (Fed. Cir. 1990); *see also, In re Fritch,* 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). This includes what could be characterized as simple changes. *See Gordon*, 221 U.S.P.Q. at 1127. Even changes that are allegedly "merely a matter of engineering design choice" require a suggestion of desirability in the prior art. *See In re Kuhle*, 188 U.S.P.Q. 7, 9 (CCPA 1975). In *Kuhle*, the element in question as the "obvious matter of design choice" was obvious because it was "notoriously old with the common flashlight." *Id.* at 8. As such, the prior art did contain a teaching that suggested the modification in question to one of ordinary skill in the art, thereby establishing a *prima facie* case of obviousness.

In the present case, the deficiencies in the teachings of Cho *et al.* regarding the specific claimed density of observed polymorphisms in *Arabidopsis* plants are not cured by Lai *et al.* Lai *et al.* may teach an SNP map in the human genome having a density of one or more polymorphisms per about 30 kb. However, the disclosure of Lai *et al.* does not in any way relate to the genome of *Arabidopsis* plants, nor does it in any way suggest that a desired density of polymorphisms in the *Arabidopsis* genome would result in the detection of more than one polymorphism per about 100 kb. As such, Lai *et al.* do not provide specific motivation to one of

ordinary skill in the art such that the skilled artisan would arrive at the present invention upon reading Cho *et al.* in view of Lai *et al.*

In sum, the Examiner's conclusion of obviousness is based on improper hindsight reasoning. No suggestion to modify the cited references has been found in the cited references or pointed out to Applicant from the general knowledge of one of ordinary skill in the art. For at least these reasons, the Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness, as required by 35 U.S.C. § 103. As such, withdrawal of this rejection is respectfully requested.

B. Rejection over Cho *et al.* in view of Lai *et al.* and further in view of Davis *et al.*

Claims 1-3, 5, 10-12, 15-16, 27, and 35 stand rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Cho *et al.* in view of Lai *et al.* and further in view of Davis *et al.* This rejection is respectfully traversed and reconsideration is requested for at least the reasons that follow.

Davis *et al.* teach methods in which positional cloning is used to localize and isolate a regions of genomic DNA associated with a phenotype of interest. Regardless of whatever else Davis *et al.* do disclose, Davis *et al.* do not provide any teachings or motivation to one of skill in the art with regarding to the claimed density of polymorphisms. Therefore, for the reasons stated above with regard to the rejection over Cho *et al.* in view of Lai *et al.*, the cited references do not render the present independent claims obvious since specific limitations of the claims are neither taught nor suggested by the cited references. The cited references do not disclose or suggest an SNP map of *Arabidopsis* with a density of more than one polymorphism per about 100 kb.

More specifically, claim 12 is directed to Single Nucleotide Polymorphism 471736. The Examiner has not indicated where Single Nucleotide Polymorphism 471736 is disclosed in Cho *et al.*, Lai *et al.*, or Davis *et al.* Therefore, for at least this additional reason, Cho *et al.*, Lai *et al.*, and Davis *et al* , alone or in combination, do not render claim 12 obvious.

For at least these reasons, it is submitted that the present claims are patentable over Cho *et al.*, Lai *et al.*, and Davis *et al.*, and withdrawal of this rejection is respectfully requested.

C. Rejection over Cho *et al.* in view of Somerville

Claims 1-7, 10-12, 15-17, and 27-35 stand rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Cho *et al.* in view of Somerville. This rejection is respectfully traversed for at least the reasons which follow.

The Examiner again notes that "Cho *et al.* do not teach a method wherein the polymorphisms are distributed throughout the genome of Arabidopsis plants at an average density of more than one polymorphism per about 100 kb." *Office Action at page 6.* However, in support of this rejection, the Examiner asserts that "Somerville discloses the availability of a dataset that represent more than 35,000 polymorphisms in the Arabidopsis genome, and provides instruction as to how to access the database for use in 'the isolation of genes in map based cloning, among other things.' Single Nucleotide Polymorphism 471736 is presumed to be a member of this large set of polymorphisms." *Id.* As indicated by the Examiner, Somerville does not actually disclose the dataset, and does not teach a method wherein the polymorphisms are distributed throughout the genome of *Arabidopsis* plants at an average density of more than one polymorphism per about 100 kb. In addition, the Examiner admits that the inclusion of Single Nucleotide Polymorphism 471736 in the database is only a presumption and offers no concrete evidence that one of ordinary skill in the art would recognize such inclusion upon reading Somerville.

Applicants respectfully submit that the disclosure of Somerville does not provide adequate enabling teaching of the present invention. Somerville merely mentions the existence of a dataset and does not in any way provide a public disclosure sufficient to provide a teaching to one of ordinary skill in the art such that the skilled artisan is enabled or motivated to modify the teachings of Cho *et al.* in a manner which renders the present invention obvious. As such, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is now in condition for allowance, and notice of such is respectfully

requested. The Examiner is encouraged to contact the undersigned at (202) 942-5000 should any additional information be necessary for allowance.

Respectfully submitted,

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Date: July 24, 2002

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Marked Up Version of the Specification

Page 2, lines 13-25:

Identification of target loci and the isolation of associated genes using molecular markers has been reported (Liu *et al., Proc. Natl. Acad. Sci. USA, 96*:6535-6540 (1999); Muramoto *et al., The Plant Cell, 11*:335-347 (1999); Bowman and Smyth, *Development, 126*:2387-2396 (1999); Michaels and Amasino, *The Plant Cell, 11*:949-956 (1999); Ha *et al., The Plant Cell, 11*:1153-1163 (1999); Walker *et al., The Plant Cell, 11*:1337-1349 (1999); Sedbrook *et al., Proc. Natl. Acad. Sci. USA, 96*:1140-1145 (1999); Kiyosue *et al., Proc. Natl. Acad. Sci. USA, 96*:4186-4191 (1999); and Davis *et al., Proc. Natl. Acad. Sci. USA, 96*:6541-6546 (1999), all of which are herein incorporated by reference in their entirety). The use of markers to isolate a genomic region of interest is often referred to as map based cloning, chromosome walking or positional cloning. Many of the *Arabidopsis thaliana* markers that have been used in map based cloning are anchored to genetic maps such as the Lister & Dean map (*See e.g.* [http://genome-www3.stanford.edu/ cgi-bin/AtDB/ Riintromap] genome-www3.stanford.edu/ cgi-bin/AtDB/ Riintromap).

Page 2, line 26 to page 3, line 7:

Physical or partial physical maps of the *Arabidopsis thaliana* genome have also been reported (*See e.g.* [http://genome-www3.stanford.edu/atdb_welcome.html] genome-www3.stanford.edu/atdb_welcome.html). A physical map of *Arabidopsis thaliana*, Columbia based on a collection of bacterial artificial chromosomes (BACs) is available (Marra *et al., Nat. Genet., 22(3)*:265-270 (1999); Mozo *et al., Nat. Genet., 22(e)*:271-275 (1999), both of which are herein incorporated by reference in their entirety). An overlapping series of BACs representing the *Arabidopsis thaliana*, Columbia genome is available from AIMS, Arabidopsis Biological Resource Center, 309 B&Z Building, 1735 Neil Avenue, Columbus, OH 43210, USA.

Page 8, line 24 to page 9, line 14:

The primers herein are selected to be "substantially" complementary to the different strands of each specific sequence to be amplified. This means that the primers must be sufficiently complementary to hybridize with their respective strands. Therefore, the primer sequence need not reflect the exact sequence of the template. For example, a non-complementary nucleotide fragment may be attached to the 5' end of the primer, with the remainder of the primer sequence being complementary to the strand. Alternatively, non-complementary bases or longer sequences can be interspersed into the primer, provided that the primer sequence has sufficient complementarity with the sequence of the strand to be amplified to hybridize therewith and thereby form a template for synthesis of the extension product of the other primer. Computer generated searches using programs such as Primer 3 ([www.genome.wi.mit.edu/cgi-bin/primer/primer3.cgi] www.genome.wi.mit.edu/cgi-bin/primer/primer3.cgi), STSPipeline ([www-genome.wi.mit.edu/cgi-bin/www-STS_Pipeline] www-genome.wi.mit.edu/cgi-bin/www-STS_Pipeline), or GeneUp (Pesole *et al., BioTechniques 25*:112-123 (1998), the entirety of which is herein incorporated by reference), for example, can be used to identify potential PCR primers. Exemplary primers include primers that are 18 to 50 bases long, where at least between 18 to 25 bases are identical or complementary to at least 18 to 25 bases of a segment of the template sequence.

Page 17, line 25 to page 19, line 12:

SNPs can be characterized using any of a variety of methods. Such methods include the direct or indirect sequencing of the site, the use of restriction enzymes (Botstein *et al., Am. J. Hum. Genet. 32*:314-331 (1980), the entirety of which is herein incorporated by reference; Konieczny and Ausubel, *Plant J. 4*:403-410 (1993), the entirety of which is herein incorporated by reference), enzymatic and chemical mismatch assays (Myers *et al., Nature 313*:495-498 (1985), the entirety of which is herein incorporated by reference), allele-specific PCR (Newton *et al., Nucl. Acids Res. 17*:2503-2516 (1989), the entirety of which is herein incorporated by reference; Wu *et al., Proc. Natl. Acad. Sci. USA 86*:2757-2760 (1989), the entirety of which is

herein incorporated by reference), ligase chain reaction (Barany, *Proc. Natl. Acad. Sci. USA 88*:189-193 (1991), the entirety of which is herein incorporated by reference), single-strand conformation polymorphism analysis (Labrune *et al., Am. J. Hum. Genet. 48*:1115-1120 (1991), the entirety of which is herein incorporated by reference), single base primer extension (Kuppuswamy *et al., Proc. Natl. Acad. Sci. USA 88*:1143-1147 (1991), Goelet US 6,004,744; Goelet 5,888,819; all of which are herein incorporated by reference in their entirety), solid-phase ELISA-based oligonucleotide ligation assays (Nikiforov *et al., Nucl. Acids Res. 22*:4167-4175 (1994), dideoxy fingerprinting (Sarker *et al., Genomics 13*:441-443 (1992), the entirety of which is herein incorporated by reference), oligonucleotide fluorescence-quenching assays (Livak *et al., PCR Methods Appl. 4*:357-362 (1995a), the entirety of which is herein incorporated by reference), 5'-nuclease allele-specific hybridization TaqMan™ assay (Livak *et al., Nature Genet. 9*:341-342 (1995), the entirety of which is herein incorporated by reference), template-directed dye-terminator incorporation (TDI) assay (Chen and Kwok, *Nucl. Acids Res. 25*:347-353 (1997), the entirety of which is herein incorporated by reference), allele-specific molecular beacon assay (Tyagi *et al., Nature Biotech. 16*:49-53 (1998), the entirety of which is herein incorporated by reference), PinPoint assay (Haff and Smirnov, *Genome Res. 7*:378-388 (1997), the entirety of which is herein incorporated by reference), dCAPS analysis (Neff *et al., Plant J. 14*:387-392 (1998), the entirety of which is herein incorporated by reference), pyrosequencing (Ronaghi *et al, Analytical Biochemistry 267*:65-71 (1999); Ronaghi *et al* PCT application WO98/13523; Nyren *et al* PCT application WO 98/28440, all of which are herein incorporated by reference in their entirety; [http//www.pyrosequencing.com] www.pyrosequencing.com), using mass spectrometry *e.g.*, the Masscode ™ system (Howbert *et al* WO 99/05319; Howber *et al.* WO 97/27331, all of which are herein incorporated by reference in their entirety; [http/www.rapigene.com] www.rapigene.com; Becker *et al* PCT application WO 98/26095; Becker *et al* PCT application; WO 98/12355; Becker *et al.* PCT application WO 97/33000; Monforte *et al* US 5,965,363, all of which are herein incorporated by reference in their entirety), invasive cleavage of oligonucleotide probes (Lyamichev *et al Nature Biotechnology 17*:292-296, herein incorporated by reference in its entirety; [http//www.twt.com] www.twt.com), using high density oligonucleotide arrays

(Hacia *et al. Nature Genetics 22*:164-167; herein incorporated by reference in its entirety; [http//www.affymetrix.com] www.affymetrix.com).

Page 47, lines 16-25:

PHRED is used to call the bases from the sequence trace files ([http://www.mbt.washington.edu] www.mbt.washington.edu). PHRED uses Fourier methods to examine the four base traces in the region surrounding each point in the data set in order to predict a series of evenly spaced predicted locations. That is, it determines where the peaks would be centered if there are no compressions, dropouts, or other factors shifting the peaks from their "true" locations. Next, PHRED examines each trace to find the centers of the actual, or observed peaks and the areas of these peaks relative to their neighbors. The peaks are detected independently along each of the four traces so many peaks overlap. A dynamic programming algorithm is used to match the observed peaks detected in the second step with the predicted peak locations found in the first step.

Page 48, lines 3-12:

Contigs are assembled using PANGEA clustering tools (PANGEA SYSTEMS. INC) and PHRAP ([http://www.mbt.washington.edu] www.mbt.washington.edu). PANGEA clustering tools are a series of scripts which group sequences (clusters) by comparing pairs of sequences for overlapping bases. The overlap is determined using the following high stringency parameters: word size = 8; window size = 60; and identity is 93%. Each of the clusters are then assembled using PHRAP. The final assembly output contains a collection of sequences including contigs, sequences representing the consensus sequence of overlapping clustered sequences, and singletons, sequences which are not present in any cluster of related sequences. Collectively, the contigs and singletons resulting from a DNA assembly are referred to as islands.

Page 49, line 14 to page 49, line 11:

INDELs are identified by aligning sequences from *Arabidopsis thaliana*, Columbia and *Arabidopsis thaliana*, Landsberg *erecta*. Finished BAC sequences derived from *Arabidopsis thaliana*, Columbia are obtained from GenBank ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide] www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide). Because the GenBank sequences are subject to change, the finished sequences of the *Arabidopsis thaliana*, Columbia BACs are included herein as SEQ ID NO: 1 through SEQ ID NO: 124. The sequence of each *Arabidopsis thaliana*, Columbia BAC is used as a query against a database of *Arabidopsis thaliana*, Landsberg *erecta* islands using the GAP2 program of the Analysis and Annotation Tool (AAT) for Finding Genes in Genomic Sequences which was developed by Xiaoqiu Huang at Michigan Tech University and is available at the web site [http://genome.cs.mtu.edu/] genome.cs.mtu.edu/. See Huang, *et al., Genomics 46*:37-45 (1997) and Huang, *Computer Applications in the Biosciences 10* 227-235 (1994), both of which are herein incorporated by reference in their entirety. The GAP2 program compares the query sequence with a cDNA database using a fast database search program and a rigorous alignment program. The database search program quickly identifies regions of the query sequence that are similar to a database sequence. Then the alignment program constructs an optimal alignment for each region and the database sequence. The output file of GAP2 is reviewed for insertions or deletions. Using alignments that are at least 96% identical (as reported by AAT), insertions and deletions are determined by looking for gaps of at least three bases, with three aligned bases on either side of the gap. To ensure that an insertion or deletion is derived from matched sequence, the 10bp region to either side of the gap is aligned and compared. To be considered an insertion or deletion, the adjacent aligned regions must be at least 90% identical (as reported by AAT). Insertions or deletions smaller than 100bp are considered candidate markers. INDELs identified by the method of this Example 2 are set forth in Table A and identified in the "method" column by reference to method 2. More particularly Table A identifies the location and nature of the polymorphism as follows.